REMARKS

Reconsideration of the Final Office Action mailed June 23, 2005, (hereinafter "instant Office Action") and withdrawal of the rejection of claims 21-27, 32 and 33 are respectfully requested.

In the instant Office Action, claims 1-88 are listed as pending, claims 1-20, 28-31 and 34-88 are withdrawn from consideration and claims 21-27, 32 and 33 are listed as rejected.

The Examiner has maintained the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for the atomic coordinates for residues 802-1124 of Tie-2 and Inhibitor III complex, does not reasonably provide enablement for the atomic coordinates of an unbound version of a Tie-2 polypeptide or atomic coordinates of the complete polypeptide of Tie-2 and Inhibitor III complex. The Examiner alleges that the invention as presently stated in claim 21 encompasses these additional sets of atomic coordinates, but that they are not included in the specification which consequently causes a lack of scope of enablement of the instant invention for one of ordinary skill in the art. Applicants respectfully traverse this rejection. Applicants maintain the arguments that were presented in the Reply mailed December 23, 2003 and the Request for Continued Examination filed September 8, 2004.

M.P.E.P. §2164.01 states:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited Charge Cell Culture Microcarriers, 221 U.S.P.Q. 1164, 1175 (Int'l Trade Comm'n 1983) aff'd sub nom *(Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985§. See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

The Examiner relies on Drenth, page 1, lines 13-20 as evidence that the science of protein crystallization is well know to be a trial and error procedure with unpredictable results. Applicants respectfully point out that at lines 8-35 on page 2 Drenth describes the four steps involved in crystallizing proteins. Drenth provides examples of what is known, such as in page 2, lines 23-24 "[t]he energy barrier is easier to overcome at a higher level of supersturation". Drenth also confirms Applicants' argument that one may need to adjust different parameters in the crystallization process in order to produce crystals. For example, in discussing how to

achieve the proper level of supersaturation, at lines 41-42 on page 2 Drenth states "[t]he easiest way to change the degree of supersaturation is by changing the temperature." This implies that there are other ways to adjust the level of supersaturation and that one skilled in the art knows what those ways are. At line 43 on page 2 Drenth states "[p]recipitation of the protein can be achieved in more than one way." Further, at page 3, lines 38-42, Drenth summarizes "the usual procedure for crystallizing a protein". Further, at line 45, page 3 to line 1, page 4 Drenth writes that is it usually necessary to carry out a great number of experiments. The fact that Drenth points out that there is a standard procedure for crystallizing a protein, that it may be necessary to vary different parameters, how to do so in order to obtain said crystal and that it will normally take multiple experiments to crystallize a protein supports Applicants' position that 1) one of ordinary skill in the art would know to vary different conditions in order to obtain crystals and 2) that this is routine experimentation in the art of protein crystallization and it is not undue.

The instant specification teaches crystallization conditions for diphosphorylated Tie-2 802-1124 on page 48, Tie-2 (D964N) 802-1124 (SEQ ID NO 1)on page 49 and for Tie-2 (D964N) 802-11234 (SEQ ID NO 2) on page 51 of the instant application. Further, Table II on pages 53-56 lists crystallization conditions for Tie-2/inhibitor complexes. Applicants have provided the crystallization conditions such as protein concentration, buffer concentration, pH, buffer identity, precipitant and additive parameters to enable one of ordinary skill in the art to crystallize the protein.

Thus, through examples and teachings throughout the instant specification Applicants have enabled the instant invention. Applicants have taught all of the steps of claim 21 and enabled others to utilize the claimed method to identify compounds which are inhibitors of a Tie-2 protein.

Based upon the foregoing, the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, for lack of scope enablement is obviated and should be withdrawn.

The Examiner has maintained the rejection of Claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the invention was filed, had possession of the claimed invention. The Examiner alleges that "due to the open claim language of 'comprises' in claim 21, this claim is directed to encompass amino acid sequences that do not meet the written description provision of

35 U.S.C. §112, first paragraph." Applicants respectfully traverse this rejection. Applicants maintain the arguments presented in the Replies filed December 23, 2003 and January 10, 2005.

The Examiner admits that Applicants have provided atomic coordinates for the catalytic domain of Tie-2 (residues 802-1124). Claim 21 is directed to a method of identifying a compound which is an inhibitor of Tie-2 protein. Step (a) of claim 21 is to obtain the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein. As Applicants describe at lines 21-25, page 3 of the instant specification:

> In another embodiment, the method for identifying a compound which inhibits the catalytic activity of Tie-2, comprises the step of determining the ability of one or more functional groups and/or moieties of the compound, **when present in, or bound to, the Tie-2 catalytic domain, to interact with one or more subsites of the Tie-2 catalytic domain**. (emphasis added)

Applicants respectfully point out that in order for a compound to inhibit a Tie-2 protein, one or more functional groups and/or moieties of the compound must be present in or bound to the Tie-2 catalytic domain. Thus, the catalytic domain of Tie-2 (residues 802-1124) must be present in order for a compound to inhibit the Tie-2 protein. Therefore, so long as the catalytic domain of Tie-2 is present, it does not matter whether it is the unbound Tie-2 polypeptide or the entire Tie-2 polypeptide and inhibitor III complex is being used. Only the catalytic domain of Tie-2 is essential for claim 21.

With respect to the rejection of claim 27, as the Examiner pointed out, the term "comprising" is open claim language. In claim 27 "comprising" refers to the polypeptide containing at least (i.e. at a minimum) the catalytic domain of Tie-2. Whether it is the unbound Tie-2 polypeptide or the entire Tie-2 polypeptide and inhibitor III complex is being used is not relevant so long as the catalytic domain of Tie-2 is present.

Based upon the foregoing, the rejection of Claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention, is obviated and should be withdrawn.

The Examiner has maintained the rejection of claims 21, 22 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack*

(703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)). Applicants respectfully traverse this rejection and maintain the arguments presented in the Reply filed December 23, 2003 and the Request for Continued Examination filed September 8, 2004.

Applicants respectfully point out that that M.P.E.P. §2142 states the following with respect to obviousness:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Obtaining the crystal coordinates is one of the steps of Applicant's claim. Without those coordinates one is unable to utilize the method of claim 21.

In the RCE filed January 10, 2005, Applicants pointed out that Chen et al. also do not teach or suggest the step of obtaining the atomic coordinates of a Tie-2 protein. In the instant Office Action, the Examiner states "[t]his statement is found unpersuasive as the atomic coordinates are considered nonfunctional descriptive material, such that Chen et al. in view of *In re Gulack* suggests this step." In fact, in *In re Gulack*, the CCPA found that the printed matter could be accorded patentable weight if there exists a functional relationship between the printed matter and the substrate. In the instant invention, the atomic coordinates of the crystal of the polypeptide are functionally related to the method of claim 21 because the atomic coordinates identify the active subsites of Tie-2, which in turn allows one to identify or design an inhibitor of Tie-2. A compound which interacts with a preselected number or set of subsites, said subsites having been identified using the atomic coordinates of the crystal of the polypeptide, or has a calculated interaction energy within a desired or preselected range, the compound is identified as a potential inhibitor of Tie-2. Thus, the atomic coordinates are not nonfunctional descriptive matter but an integral piece of information required to select or design inhibitors. The coordinates are equivalent to a drawn chemical structure. Without the coordinates one cannot envision the structure of the Tie-2 protein or identify compounds which will bind to the specific active subsites. Without the atomic coordinates, one would not be able to design a compound made to inhibit the Tie-2 protein. The details of docking results depend intimately from the functional results computed from these coordinates. Using the atomic coordinates in this way is functionally equivalent to ascertaining the structure of an organic compound and using it as a

basis for making further analogs. The atomic coordinates are not separable from the method of designing the inhibitor.

In addition, Chen et al. teaches interaction with four domains of STAT: an α-helical domain, a DNA binding domain, a SH2 domain and a linking domain that links the DNA binding domain to the SH2 domain. There is no teaching or suggestion of the catalytic domain of Tie-2 or designing or identifying compounds that bind to the catalytic domain.

Based upon the foregoing, the rejection of claims 21, 22 and 26 under 35 U.S.C. §103(a) over Chen et al. in view of *In re Gulack* is obviated and should be withdrawn.

The Examiner has maintained the rejection of claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) and Ziegler (P/N 5,447,860). Applicants respectfully traverse this rejection and maintain the arguments presented in the Replies filed December 23, 2003 and January 10, 2005.

The Examiner found unpersuasive Applicant's statement that Ziegler refers to the biological ligand of Tie that binds to the extracellular domain, not the small molecule ligands that bind to the catalytic domain of Tie-2. The Examiner states:

> This statement is unpersuasive as the instant claims, such as instant claim 21, do not state that the compound must bind to the catalytic domain of Tie-2. Instead the compound must simply bind to one or more active subsites (note that the first line of step (c) in instant claim 21, do not state that the compound must bind to the catalytic domain of Tie-2.

Applicants respectfully direct the Examiner's attention to page 3, lines 21-25 of the instant specification wherein Applicants state:

> In another embodiment, the method for identifying a compound which inhibits the catalytic activity of Tie-2, comprises the step of determining the ability of one or more functional groups and/or moieties of the compound, when present in, or bound to, the Tie-2 catalytic domain, to interact with one or more subsites of the Tie-2 catalytic domain.

Thus, Applicants teach that the compound binds to one or more active subsites of the Tie-2 catalytic domain. Since claims are read in light of the specification, it is clear that in the method of claim 21 compounds bind to the Tie-2 catalytic domain. There is no

teaching, suggestion or motivation in Ziegler for compounds to bind to the catalytic domain of Tie-2.

Based upon the foregoing, the rejection claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPW 430) and *In re Fitzgerald* (205 USPQ 594) and Ziegler (P/N 5,447,860) is obviated and should be withdrawn.

The Examiner has maintained the rejection of claims 21-27 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (P/N 6,160,092) in view of Vikkula et al. (Cell, 1996, Volume 87, pages 1181-1190) and In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594). Applicants respectfully traverse this rejection and maintain the arguments presented in the Replies filed December 23, 2003 and January 10, 2005.

The Examiner has not established a *prima facie* case of obviousness in any of the foregoing rejections. The same arguments as made above in response to the rejections of claims 21, 22 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)) and claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) apply to this rejection as well.

The combination of Chen et al. in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) does not suggest a method of identifying compounds that inhibit a Tie-2 protein using crystal coordinates to define the active subsites of Tie-2 and identifying a compound which binds to one or more of these active subsites in the catalytic domain. Chen et al. teaches interaction with four domains of STAT: an α-helical domain, a DNA binding domain, a SH2 domain and a linking domain that links the DNA binding domain to the SH2 domain. Vikkula et al., on the other hand, discloses that mutations in the kinase domain of Tie-2 result in increased activity of Tie-2 and that an activating mutation in Tie-2 causes venous malformations. The combination of Vikkula et al. with Chen et al (P/N 6,160,092) do not teach or suggest Applicants' method of obtaining atomic coordinates comprising the catalytic domain of Tie-2 and using said atomic coordinates to obtain a compound that is an inhibitor of a Tie-2 protein.

Based upon the foregoing, Applicants believe the rejection of claims 21-27 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (P/N 6,160,092) in view of Vikkula et al. (Cell, 1996, Volume 87, pages 1181-1190) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) is obviated and should be withdrawn.

No fees are due for the instant amendment since the total number of claims after entry of the amendments hereinabove is not more than the total number of claims that Applicants have paid for to date.

Based upon the foregoing, Applicants believe that claims 21-27, 32 and 33 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

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Gayle O'Brien

Gayle B. O'Brien
Agent for Applicants
Reg. No. 48,812

Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
(508) 688-8053